IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC., Plaintiff, v. MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC., Defendants.	C.A. No. 22-cv-228 (RGA) (JLH) (Consolidated)

DEFENDANTS' REPLY POST-TRIAL BRIEF ON INVALIDITY

OF COUNSEL:

George C. Lombardi
Bryce A. Cooper
Kurt A. Mathas
Elizabeth E. Grden
Kevin J. Boyle
Brian L. O'Gara
WINSTON & STRAWN LLP
35 W. Wacker Drive
Chicago, IL 60601-9703
(312) 558-5600

HEYMAN ENERIO
GATTUSO & HIRZEL LLP
Dominick T. Gattuso (#3630)
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@hegh.law

Attorneys for Defendants
MSN Laboratories Private Limited and
MSN Pharmaceuticals, Inc.

Dated: February 20, 2024

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

TABLE OF ABBREVIATIONS

Term	Definition
'015 patent	U.S. Patent No. 11,098,015 (JTX-003)
'349 patent	U.S. Patent No. 11,298,349 (JTX-004)
'439 patent	U.S. Patent No. 11,091,439 (JTX-001)
'440 patent	U.S. Patent No. 11,091,440 (JTX-002)
1-1 impurity	6,7-dimethoxy-quinoline-4-ol
API	Active pharmaceutical ingredient
Berge	Berge et al., Pharmaceutical Salts, Journal of Pharmaceutical Sciences, 66, 1-19 (1977) (DTX-166)
Brown	International Publication No. WO 2010/083414 A1, to Brown et al. (DTX-291)
Bighley	Bighley et al., Salt Forms of Drugs and Absorption, in 13 Encyclopedia of Pharmaceutical Technology 453 (James Swarbrick & James C. Boylan eds., 1995) (DTX-167) ("Bighley" is a chapter in the "Swarbrick" encyclopedia)
Cabozantinib I Case	*Exelixis, Inc. v. MSN Lab'ys Priv. Ltd.*, No. CV 19-2017-RGA-SRF (D. Del.)
DFF	Defendants' Opening Post-Trial Findings of Fact, D.I. 170
DTX	Defendants' Trial Exhibit
Exelixis	Plaintiff Exelixis, Inc.
FDA Guidance	FDA, Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, Center for Drug Evaluation and Research (February 1987) (DTX-170)
FDA GTI Guidance	FDA Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommend Approaches (DTX-091)
Gibson	Steele, Preformulation Predictions from Small Amounts of Compound as an Aid to Candidate Drug Selection, A Practical Guide from Candidate Drug Selection to Commercial Dosage Form (2001) (DTX-392)
Girindus	Girindus AG Kuensebeck
GRAS	Generally Recognized as Safe
GTI	Genotoxic Impurity
HCC	Hepatocellular carcinoma
HPLC	High-performance liquid chromatography
JTX	Joint Trial Exhibit
Lachman	Lachman et al., Pharmaceutical Dosage Forms, Second Edition, 1989 (PTX-553, which is a duplicate of DTX-288)
Malate Salt Patents	Collectively, U.S. Patent Nos. 11,091,439; 11,091,440; and 11,098,015
MSN	MSN Laboratories and MSN Pharmaceuticals
MSN Laboratories	Defendant MSN Laboratories Private Limited
MSN Pharmaceuticals	Defendant MSN Pharmaceuticals Inc.
NCCN	National Comprehensive Cancer Network

Term	Definition
POSA	Person of ordinary skill in the art
PTX	Plaintiff's Trial Exhibit
RCC	Renal cell carcinoma
Regis	Regis Technologies, Inc.
Remington's	Remington's Pharmaceutical Sciences Handbook (e.g., DTX-284)
Resp.	Exelixis' Responsive Post-Trial Brief, D.I. 175
RFOF	Exelixis' Responsive Post-Trial Findings of Fact, D.I. 176
Stahl	Stahl & Wermuth, "Monographs on Acids and Bases," in Handbook of Pharmaceutical Salts: Properties, Selection, and Use 10 (Stahl, P.H., Wermuth, C.G., eds., 2002) (PTX-610)
Swarbrick	Swarbrick et al., Encyclopedia of Pharmaceutical Technology (e.g., PTX-394)
Tong	Tong et al., In situ Salt Screening—A Useful Technique for Discovery Support and Preformulation Studies, Pharm. Dev. Technol. 3 (2), 215-223 (1998) (DTX-243)
TKI	Tyrosine kinase inhibitor
Vippagunta	Vippagunta et al., Crystalline solids, Advanced Drug Delivery Reviews, 48, 3-26 (2001) (DTX-191)
XRPD	X-ray Power Diffraction

I. INTRODUCTION

At trial and in its post-trial opening brief (D.I. 169), MSN presented clear and convincing evidence that the asserted claims of the Malate Salt Patents are invalid for lack of written description and obviousness-type double patenting and that the asserted claim of the '349 patent is invalid as obvious. Exelixis' rebuttal arguments do not overcome MSN's showing.

II. LACK OF WRITTEN DESCRIPTION OF THE MALATE SALT PATENTS

Exelixis discovered two closely related crystalline forms of cabozantinib (L)-malate with similar properties, Forms N-1 and N-2. Those forms are described in the specifications of the Malate Salt Patents, but the claims are to a much broader genus that includes *any* crystalline form. The trial evidence established that Forms N-1 and N-2 do not share sufficient common structural features or other properties demonstrating that the patentees possessed an entire genus and not just two unrepresentative species in a corner of it. The patents are invalid for lack of written description.

A. The specification does not sufficiently describe possession of the claimed invention: a genus of all crystalline forms of cabozantinib (L)-malate.

The asserted claims cover *all* currently known or future-discovered crystalline forms of cabozantinib (L)-malate. DFF ¶¶ 31, 34. That defines a *genus* of crystalline salts; it does not "reinterpret" the claims. Resp. 4-5. As Dr. Trout conceded, the *scope* of the claims is the same whether the word "form" is explicitly included or not. DFF ¶ 32. And there is no question the inventors did not possess *all* crystalline forms of cabozantinib (L)-malate (DFF ¶¶ 31-51), or the full scope of the claimed genus. They only possessed the Form N-1 and N-2 species. DFF ¶ 38.

Exelixis nevertheless argues the claims do not cover a genus by conflating what it would take to prove *infringement* with what is required for adequate *written description*. Resp. 10-12. It is true that a POSA could determine whether a sample of cabozantinib (L)-malate is crystalline or amorphous—and therefore infringes the claims—without also identifying its polymorphic form.

But a crystalline salt *exists* in a polymorphic form whether or not a POSA performs the routine experiment to identify it. DFF ¶ 20. Exelixis also argues that one "aspect" of the specification relates to differentiating between crystalline and amorphous salts and a second relates to differentiating between crystalline Forms N-1 and N-2. But that too has no bearing on what the asserted claims cover. As used in the claims, the term "crystalline"—whether an "adjective" or not—*captures* all crystalline cabozantinib (L)-malate polymorphs within the claims' scope.

Tellingly, even the cases Exelixis argues are "analogous" (Resp. 13) recognize that the claims at issue are genus claims. *See GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 2013 WL 4082232, at *1, 4 (D. Del.), *aff'd* 744 F.3d 725 (Fed. Cir. 2014) ("*GSK*") ("[dutasteride] or a pharmaceutically acceptable solvate thereof" is a genus claim); *Merck Sharp & Dohme, LLC v. Mylan Pharms. Inc.*, 2022 U.S. Dist. LEXIS 195204, at *13, 100 (N.D. W.Va.) ("*Merck*") ("[DHP] salt of [sitagliptin] or a hydrate thereof" is a genus claim). Exelixis' attempt to avoid written description scrutiny by contending the asserted claims do not cover a genus should be rejected.

B. The specification does not sufficiently describe representative species of the claimed crystalline cabozantinib (L)-malate genus.

The specification does not describe all crystalline forms of cabozantinib (L)-malate, so the Malate Salt Patents are only valid if they disclose (i) "structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus" or (ii) "a representative number of species falling within the scope of the genus." *Ariad Pharms. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350-51 (Fed. Cir. 2010). The specification fails on both counts.

1. The specification does not describe sufficient common structural features shared by all crystalline forms of cabozantinib (L)-malate.

Sufficient written description for a genus requires "more than a generic statement of an invention's boundaries," because "merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and

showing that one has invented a genus and not just a species." *Id.* at 1349-50. The Federal Circuit has explained that the required "precise definition" *could* include reference to specific "structure, formula, chemical name, physical properties, or other properties" of the species falling within the genus. *Id.* at 1350. But "each case involving the issue of written description must be decided on its own facts." *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1377 (Fed. Cir. 2017).

Exelixis argues that all crystalline forms of cabozantinib (L)-malate, including Forms N-1 and N-2, have the same chemical name, formula, and "crystalline" (as opposed to amorphous) character. Resp. 13. But that merely re-states the broadly claimed genus; crystalline cabozantinib (L)-malate salts is the outer "fence" drawn by the patentees. Exelixis has not identified any common structural features or properties that establish the patentees invented the entire genus and not just two unrepresentative species in a "corner" of it. *See AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014) ("[A]nalogizing the genus to a plot of land, if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus.").

Merely identifying a claimed common chemical name and formula is not sufficient for a broad genus whose species have dissimilar features. *See In re Entresto*, 2023 WL 4405464, at *22 (D. Del.). Exelixis argues that the claim in *Entresto* covered two "dissimilar subgenera" ("combinations" and "complexes" of active ingredients), whereas all crystalline cabozantinib (L)-malate forms have the "same basic structural characteristics." Resp. 15. But Exelixis' conclusory distinction is not supported by the evidence. Both the crystalline structures and physico-chemical properties of the 11 known crystalline cabozantinib (L)-malate species vary significantly. *See* DFF ¶¶ 41-42, 56-62. Exelixis also cannot distinguish *Entresto* based on whether "the alleged genus clearly existed as of the priority date." Resp. 15. The *genus* exists in both cases. It is the *species*

within it—complexes in *Entresto* and all other crystalline forms here—that are completely unknown, with properties dissimilar to the disclosed species. The *Entresto* analysis is on point.

By contrast, Exelixis' reliance on *GSK* is misplaced. The patent in *GSK* claimed dutasteride "or a pharmaceutically acceptable solvate thereof," which included three solvate "subgroups": crystalline, precipitated, and reacted. 2013 WL 4082232, at *2, *4. The specification only disclosed an example of the crystalline form, but this Court found that sufficient, reasoning "the universe of solvents thought to be pharmaceutically acceptable was well-known and relatively small" and that the "language of the specification itself suggests that any one of the solvate forms will suffice equally." *Id.* at *5-6. This case is not analogous.

First, when GSK sought claims to "pharmaceutically acceptable solvate[s]" of dutasteride, a POSA would have already been aware of the universe of potential "safe" solvents and, therefore, able to "visualize" the various species within the claimed genus. *Id.* at *6.[1] By contrast, the universe of crystalline cabozantinib (L)-malate salts at the priority date was completely unknown and—according to Exelixis' expert—"virtually infinite." DFF ¶¶ 35, 64.

Second, in *GSK* there was "no dispute that a[ny] solvate of dutasteride has the same effective chemical function of dutasteride." 2013 WL 4082232 at *6. While there were no claimed "functional" limitations, a POSA would face "less uncertainty" envisioning the genus if there is no "correlation" between the species' structural characteristics and functions. *Id.* There is no parallel here. The trial evidence established that the physico-chemical properties and functions of crystalline cabozantinib (L)-malate salts differ—often dramatically—depending on their different

[1] As this Court noted, "the concept of solvation … has been known in the art for over 100 years." 2013 WL 4082232 at *6. The dutasteride compound was "where the novelty lies, and that is where a person skilled in the art would need the most information." *Id.* Here, of course, there was no novelty in the compound as it was already disclosed in the prior art. DFF ¶ 66.

crystal structures. DFF ¶¶ 52-54, 63. And it is undisputed that not all crystalline forms will share the "beneficial properties" that the specification touts for Forms N-1 and N-2. DFF ¶¶ 39-51.

Third, all claimed species in *GSK* were created by a process identified in the specification: simply "dissolving dutasteride (the solute) in a solvent." 744 F.3d at 730. Exelixis argues that the Malate Salt Patents' specification similarly "provides a detailed description of how the claimed material … could be prepared." Resp. 14. But that specification only describes how to make Forms N-1 and N-2. Tr. 904:19-23 (Trout). It is undisputed that every other species in the genus would be prepared by methods that are not disclosed. DFF ¶¶ 44-45.[2]

2. The specification does not describe a representative number of crystalline forms of cabozantinib (L)-malate.

The standard for what constitutes a representative number of examples in a genus will "necessarily vary depending on the context." *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1359 (Fed. Cir. 2019). Considering the technology here, Exelixis is wrong both about the size of the claimed genus and whether Forms N-1 and N-2 are representative of the species within it.

a. The crystalline cabozantinib (L)-malate genus is very broad.

Exelixis first claims there is no basis that the genus here is potentially infinite. Resp. 16. But its own expert confirmed it: for any crystalline compound, "[t]he range and combinations of

[2] This case is not analogous to *BMS v. Aurobindo Pharma USA Inc.*, 477 F. Supp. 3d 306 (D. Del. 2020), for the same reason. In *BMS*, preparation methods for *all* claimed species of "pharmaceutically acceptable salts of [apixaban]" were disclosed. *Id.* at 353. And in non-binding *Merck*, disclosure of one hydrate of a DHP salt of sitagliptin provided sufficient disclosure for the claimed genus of all hydrates of the salt. 2022 U.S. Dist. LEXIS 195204, at *105. But unlike here, there was no evidence that any other hydrate species existed. *Id.* Nor did the Court identify any evidence—similar to the facts presented in *GSK*—that any other potential hydrate species within the claimed genus would have different physico-chemical or functional properties. *Id.*

crystal growth structures are virtually infinite." Tr. 922:12-17 (Trout); *see also* DFF ¶ 35.[3]

Exelixis also disputes the number of known forms of crystalline cabozantinib (L)-malate. Resp. 16-17. But the trial evidence established that at least 11 distinct forms exist—and Dr. Trout agreed before his about-face at this trial. Tr. 915:5-16. Dr. Steed introduced patent literature with characterization data and preparation methods for each of them. Tr. 455:23-460:3; DFF ¶¶ 40-42.[4] And he walked the Court through his analysis, utilizing multiple examples and demonstratives, establishing that all 11 forms were unique. Tr. 455:23-460:3; DDX(Steed)-19, 20, 21.

Exelixis' critique that Dr. Steed did not spend more time showing every form is curious in view of its own trial presentation. Resp. 17. Dr. Trout compared XRPDs of two samples of cabozantinib free base (called "Form M" in MSN's U.S. Patent No. 11,261,160). Tr. 861:23-864:23; PDX-6.15; *see also* Resp. 18. But this testimony was "just irrelevant," because Dr. Steed never testified that Form M was a crystalline form. Tr. 864:22-23 (Court). The only crystalline form Dr. Trout discussed was Mylan's Form M_1, concluding it was "not clear that it's a new form." Tr. 864:24-866:1. He conceded "there's some kind of crystalline material" in Form M_1 but could not say what it was. Tr. 865:6-14. He then summarily dismissed all other forms without further analysis or explanation. Tr. 865:19-866:1. This does not rebut Dr. Steed's convincing testimony.

Exelixis now also argues there are "overlapping" peaks in the 11 different diffractograms.

---

[3] Exelixis also attempts to narrowly portray the genus by claiming "that the maximum number of polymorphic forms identified for any compound in history is fourteen." Resp. 16. But Dr. Steed explained that number referred to pure forms "characterized by single crystal crystallography," a "very high standard of characterization," and did not include solvates. Tr. 545:19-547:1, 561:20-562:7. The asserted claims are not limited to pure forms of crystalline cabozantinib (L)-malate and could include solvates, further highlighting the breadth and dissimilarity of the covered species.

[4] Dr. Steed testified that he reviewed the characterization data and preparation methods for all 11 reported forms, and they were all admitted into evidence. Tr. 455:23-456:12; JTX-0009.35 (Forms N-1, N-2); DTX-333.01 (MSN Form S); PTX-256.01 and DTX-222.01 (Mylan Forms M1, M2, M3, M4); DTX-121.05-.06 (Cipla Forms C2, C3, C4, C5).

Resp. 18. But Dr. Steed offered unrebutted testimony that it is normal and not surprising to identify some overlapping peaks when comparing XRPD diffractograms of different crystalline forms. DFF ¶ 43. Indeed, it is undisputed that Forms N-1 and N-2 are unique but share many overlapping peaks. *See* JTX-1.38, Table 2 (*compare* Compound (I) Form N-1 *to* Compound (I) Form N-2).[5]

Exelixis compares apples to oranges when it contrasts this case to others based on the raw number of known species. Resp. 18. The trial evidence established that the genus of crystalline cabozantinib (L)-malate salts is very broad for the technology at issue and potentially limitless.

b. Forms N-1 and N-2 are not representative.

Exelixis and Dr. Trout do not dispute that the crystal structures and physico-chemical properties of Forms N-1 and N-2 are: (i) not predictive of other crystalline forms (DFF ¶¶ 50-54); (ii) different from other known crystalline forms (DFF ¶¶ 56-62); and (iii) may affect the manufacturability, performance, and quality of a drug product in ways that are different from other crystalline forms (DFF ¶ 63). That should end the representativeness inquiry.

Exelixis now disputes that the known forms also include solvates. Resp. 20. But Dr. Steed's testimony that existing forms include solvates and hydrates—further emphasizing structural differences between species—went unrebutted at trial. Tr. 464:15-23, 562:8-11; *see Alza Corp. v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 622 (D. Del. 2009). That the patentees did not explicitly identify "solvates" in their patent literature is also a red herring. Resp. 20. A POSA would

[5] Exelixis contends that Dr. Steed "failed to meet his own standards" classifying crystalline forms because he purportedly previously testified that "polymorphic forms *could only* be differentiated based on XRPD data using an analysis of the ten strongest peaks." Resp. 17, citing Tr. 549:7-549:24. But the transcript clearly does not say that. Dr. Steed agreed that a POSA "*may need* to identify the ten strongest peaks in the XRPD diffractogram," consistent with the USP's teachings, but "even that's a shorthand for looking at the entire diffraction pattern." Tr. 549:14-20. Here, Dr. Steed highlighted different claimed peaks between crystalline forms for demonstrative purposes (Tr. 456:13-458:4; DDX(Steed)-20) but confirmed he considered the entire patterns of all 11 forms, which made it "clear these are different forms to each other." Tr. 560:20-561:19.

understand that claims covering crystalline salts (such as the asserted claims here) include solvates. Tr. 444:19-445:1 (Steed). Exelixis does not contend otherwise.

Exelixis' justification for ignoring the many differences between Forms N-1 and N-2 and other crystalline forms is that the claims have no limitations to those properties nor any "functional limitations." Resp. 19. But there are no such limitations in many claims where written description was found lacking. *E.g.*, *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1376-79 (Fed. Cir. 2009); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158-60 (Fed. Cir. 1998); *Entresto*, 2023 WL 4405464, at *21-22. Courts look to these structural, "physical properties, or other properties" of species falling within a claimed genus to determine whether its members can be "visualized." *Ariad*, 598 F.3d at 1350. The disparate properties here establish that Forms N-1 and N-2 reside in an unrepresentative "corner" of the genus. *AbbVie Deutschland*, 759 F.3d at 1300; *see also Purecircle USA Inc. et al. v. SweeGen Inc. et al.*, 2024 WL 20567 at *3 (Fed. Cir. 2024) (single species not representative where "only one enzyme of the potentially vast class of UGTs" was disclosed and at least "five known enzymes" shown to "come within the scope of the claims.").

Finally, MSN's arguments are not "extreme" but rather parallel cases finding written description insufficient, such as *Entresto*, *ICU Med.*, and *Allergan*.[6] It is Exelixis whose position is "unprecedented." In no case has a court found written description sufficient for broad genus claims that capture species the patentees did not invent after having failed to prove infringement on narrower claims to species they actually invented that depend on the same specification. The Court should find the asserted claims invalid for lack of adequate written description.

[6] In response to a question posed by the Court, Dr. Steed stated that each polymorph is unique and therefore he "suppose[d]" that each one is "representative of itself," which Exelixis cites in support of its argument. Tr. 467:5-14. But neither expert offered an affirmative opinion on this broad question at trial and the Court need not reach it to resolve this case, where substantial trial evidence established that Forms N-1 and N-2 are not representative of the broadly claimed genus at issue.

III. OBVIOUSNESS-TYPE DOUBLE PATENTING OF MALATE SALT PATENTS

Obviousness-type double patenting prevents patenting a "slight variation" of an "earlier patented invention." *See Sun Pharm. Indus. v. Eli Lilly*, 611 F.3d 1381 (Fed. Cir. 2010). Here, Exelixis claimed priority to the invention of the '473 patent more than ten years ago, including its claim to cabozantinib's salts. Exelixis should not be granted an improper timewise extension through the Malate Salt Patents, which also claim a cabozantinib salt and obvious variations.

A. There are no patentably distinct differences between claim 5 of the '473 patent and claim 4 of the '439 patent.

1. Pharmaceutically acceptable salts of cabozantinib include crystalline cabozantinib (L)-malate.

Exelixis does not dispute that crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib or that claim 5 of the '473 patent literally encompasses claim 4 of the '439 patent. DFF ¶¶ 67-68. A prior genus claim may not "per se" invalidate a species claim under the obviousness-type double patenting doctrine. Resp. 38. But nor do Exelixis' cases suggest that later-claimed obvious species within a previously claimed genus are entitled to patent protection. *See, e.g.*, Resp. 23, citing *Brigham & Women's Hosp. Inc v. Teva Pharms. USA, Inc.*, 761 F. Supp. 2d 210, 224 (D. Del. 2011) ("an earlier patent claiming a large genus of pharmaceutical compounds does not preclude a later patent from claiming a species within that genus, *so long as the species is novel, useful, and nonobvious*") (emphasized portion omitted from Exelixis citation).[7]

Courts have repeatedly found species claims invalid for obviousness-type double patenting over reference genus claims. *E.g.*, *Abbvie Inc. v. M&T Kennedy Inst. of Rheumatology*, 764 F.3d

[7] Exelixis also relies improperly on the specifications of the '473 patent and the Malate Salt Patents for purported differences between the reference and asserted claims. Resp. 22-23. But they are irrelevant; the correct analysis looks to the "differences between the [asserted and reference] claims" themselves. *UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1324 (Fed. Cir. 2018).

1366 (Fed. Cir. 2014); *Magna Elecs., Inc. v. TRW Auto. Holdings Corp.*, 2015 WL 11430786 (W.D. Mich.); *Halozyme, Inc. v. Iancu*, 320 F.Supp.3d 788 (E.D. Va. 2018). MSN does not argue that the genus claim 5 of the '473 patent "anticipates" the asserted species claims. Resp. 23. There are simply no patentably distinct differences between them for the same reasons articulated by the Federal Circuit panel and en banc in *Eli Lilly & Co. v. Barr Lab'ys*, 222 F.3d 973 (Fed. Cir. 2000), *on reh'g*, 251 F.2d 955 (Fed. Cir. 2011). Exelixis should not be able to "hide behind its once-advantageous broad coverage … and argue that selecting [cabozantinib (L)-malate] from the class of compounds defined by [the '473 patent] would not have been obvious." 222 F.3d 973 at 986. The *Eli Lilly* panel's decision is not controlling, but its reasoning is instructive. It is undisputed that malate salts had been used and were known in the prior art as pharmaceutically acceptable (DFF ¶ 71), making the differences between the asserted and reference claims indistinct.

2. A POSA would have been motivated to prepare crystalline cabozantinib (L)-malate with a reasonable expectation of success.

Even if the Court were to find there is a difference between the pharmaceutically acceptable salts of cabozantinib in the genus claim 5 of the '473 patent and the crystalline cabozantinib (L)-malate species, that difference is not patentably distinct, because it would have been obvious for a POSA to prepare the crystalline malate salt with a reasonable expectation of success.

First, Exelixis disputes that a POSA would be motivated to prepare a cabozantinib salt with the false premise that she must first "abandon" the free base. Resp. 24-26. But that overstates the obviousness standard, which "does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014). And contrary to Exelixis' suggestion, the free base is not the "earlier" compound for which MSN must establish some reason to "modify" to a salt; both are claimed in claim 5 of the '473 patent. *See Merck & Co., v. Biocraft Lab'ys, Inc.*, 874 F.2d

804, 807 (Fed. Cir. 1989) ("That the '813 patent discloses a multitude [> 1,200] of effective combinations does not render any particular formulation less obvious.") Further, the prior art taught not only the common use and known advantages of using salts as API, generally (DFF ¶¶ 8, 25), but also the use of cabozantinib salts to treat kidney cancer, specifically (¶¶ 89-95). A POSA would have had clear motivation to prepare a cabozantinib salt through a routine screen.

Second, Exelixis disagrees that a POSA would have been motivated to prepare a malate salt of cabozantinib. Resp. 26-33. But its arguments are again improperly directed to whether malic acid would present "the best option" and not a suitable one. For example, Exelixis notes that malic acid and cabozantinib would not meet the "Rule of 3" guidance. Resp. 30. But it does not dispute that a POSA would have considered the "Rule of 2," which Pharmorphix used in its own salt screen, and Dr. Trout conceded was a "well-known rule of thumb" that *would have* been taken into account. DFF ¶¶ 15, 76-78. Similarly, Exelixis argues that a POSA would select stronger acids such as hydrochloride (Resp. 28-29)—but there is no dispute hydrochloride would also be included in the salt screen. Tr. 552:12-18 (Steed). That does not make malic acid nonobvious. *See Trs. of Columbia Univ. in City of N.Y. v. Illumina, Inc.*, 842 F. App'x 619, 625 (Fed. Cir. 2021) ("just because better alternatives exist in the prior art does not mean that an inferior alternative is inapt for obviousness purposes."). Tong teaches that with a difference of 2 pH units, the acid is strong enough to form a salt; an even stronger acid is not necessary. DFF ¶ 15.

The relatively infrequent use of malate salts also would not dissuade a POSA from selecting malic acid. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). The "particularized facts" here more closely parallel *Apotex* than Exelixis' cited cases where courts have rejected challenges to salt claims. Resp. 7. For example, in *Pfizer Inc. v. Mylan Pharmaceuticals Inc.*, the court rejected Mylan's attempt to invalidate claims to sunitinib malate

under a *lead compound* analysis by modifying a "structurally similar analog" disclosed in the prior art as one of 1200 possible combinations. 71 F. Supp. 3d 458, 468, 474. (D. Del. 2014). By contrast, cabozantinib is explicitly disclosed in the reference claim.[8] And while the *Mylan* court also considered the obviousness of preparing the malate salt as the "last required modification" in the lead compound analysis, it relied on evidence that salt screens were limited to "three or four options" and that malate "did not appear on the most current FDA list of approved salt forms." *Id.*

Here, both sides agreed that a POSA would include 15-20 counterions in a salt screen, and malic acid was listed among FDA-approved counterions. DFF ¶¶ 11, 71. Indeed, Stahl's recently "revised list of useful salt-forming acids and bases" provided only nine acids, including malic acid, that met the "Rule of 2" for cabozantinib and were identified as GRAS. DFF ¶ 84. Exelixis' further claim that GRAS status is irrelevant to salt-screening acid selection is not credible. Resp. 30-31. The Handbook of Pharmaceutical Salts explicitly provides a "List of Salt Formers" with "acids and bases regarded as innocuous" in which GRAS status is given. PTX-610.333, 336. While the *Mylan* court rejected defendant's argument "that testing essentially all possibilities would have been done as a matter of course," 71 F. Supp. 3d at 474, Dr. Steed explained in detail how malic acid would be selected for a screen with a "relatively limited" set of counterions. DFF ¶¶ 84-86.[9]

While Exelixis describes some (routine) variables in salt screens, it never disputes the basic

[8] In *Sanofi-Synthelabo v. Apotex Inc.*, cited by Exelixis, the Court found claims to the clopidogrel bisulfate salt nonobvious because the "[prior art] patent does not enable a [POSA] to practice clopidogrel bisulfate without undue experimentation." 492 F. Supp. 2d 353, 386 (S.D.N.Y. 2007), *aff'd*, 550 F.3d 1075 (Fed. Cir. 2008). But here, Exelixis cannot dispute that the '473 patent enables cabozantinib (L)-malate; Exelixis successfully asserted it in the *Cabozantinib I* Case.

[9] *Valeant Int'l (Barbados) SRL v. Watson Pharms., Inc*., dealt with a fundamentally different obviousness inquiry. 2011 WL 6792653, at *1, *12 (S.D. Fla.). There, the compound had "been sold since the 1980s as the bupropion hydrochloride salt" and the court found the defendant had failed to prove that "*switching* from the hydrochloride salt to the hydrobromide salt" would have been obvious. *Id*. The question here, however, is whether it would have been obvious to select the (L)-malate salt as a suitable "pharmaceutically acceptable salt" of cabozantinib.

science giving a reasonable (not "guaranteed") expectation of success a crystalline malate salt will form: (i) a compound and its counterion meeting the "Rule of 2" are expected to form a salt (DFF ¶ 15); and (ii) most salts are able to be crystallized (DFF ¶ 16). Although there is "some degree of unpredictability in salt formation … the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious." *Pfizer*, 480 F.3d at 1366.[10]

B. There are no patentably distinct differences between claim 5 of the '473 patent and claim 3 of the '440 patent or claim 2 of the '015 patent.

The additional claim limitations that crystalline cabozantinib (L)-malate be in a "pharmaceutical composition" or be used to treat kidney cancer are obvious. Exelixis presented no trial testimony undermining this conclusion. Dr. Trout did not opine on the obviousness of these limitations. And Exelixis did not even cross-examine Dr. Steed on his opinions about them. Exelixis also raised no objection at trial—as it does now (Resp. 37)—to Dr. Steed's qualifications to offer opinions on "the formation, characterization, *and use* of pharmaceutical salts." Tr. 425:22-25. His more than 30 years of experience in the pharmaceutical field provides an ample basis for his testimony (Tr. 424:25-425:5), particularly given the generality of the claim limitations rendered obvious by the '928 application. Exelixis' only argument—without any expert support—is essentially that the '928 application does not *anticipate* these limitations by "explicitly" identifying the use of crystalline cabozantinib malate to treat cancer. Resp. 36-37. But Exelixis cannot dispute that the '928 application *teaches* (i) administering pharmaceutically acceptable salts of cabozantinib such as malate salts (DFF ¶ 90); and (ii) the use of cabozantinib to treat kidney cancer

[10] Exelixis argues that the '928 publication and cabozantinib's pKa would have "pointed away" (Resp. 30, 33) from malic acid, but it does not and cannot argue this rises to the level of "teaching away," which would require that the teaching "criticize, discredit, or otherwise discourage" the claimed solution. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731,739 (Fed. Cir. 2013).

(DFF ¶ 93). None of its experts ever contended otherwise.[11] These limitations are obvious.

IV. OBVIOUSNESS OF CLAIM 3 OF THE '349 PATENT

Exelixis contends that MSN's case has "two fatal flaws," but neither withstands scrutiny. First, there is no "gap" in MSN's evidence. Dr. Lepore opined that it would have been inherent and obvious to synthesize API essentially free of the 1-1 impurity. DFF ¶¶ 135, 169. Dr. Donovan opined that it would have been obvious to formulate that API into a formulation that was essentially free of the 1-1 impurity. DFF ¶ 183. And Dr. Myerson and the specification agreed that formulating the claimed composition was routine work taught by the art. DFF ¶¶ 193-196. Second, Exelixis' challenges to Dr. Lepore's inherency and obviousness opinions also fail. Exelixis primarily faults Dr. Lepore for "disregarding" a batch manufactured by Girindus. Resp. 47. But the undisputed evidence showed Girindus deviated from the Brown Example 1 process in numerous material ways. DFF ¶¶ 163-168. When faithfully followed, Brown Example 1 necessarily produced API essentially free of the 1-1 impurity, evidenced by the Regis batches. Claim 3 is invalid as obvious.

A. The Brown Example 1 Process inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity.

There is no dispute the Regis Batches were manufactured using the Brown Example 1 process (DFF ¶¶ 119, 156–157) and that they "resulted in levels of the 1-1 impurity ranging from 22 to 44 ppm," far below the claimed limitation requiring 200 ppm or less (RFOF ¶ 48). Exelixis cannot undermine the clear showing of inherency.

1. The Girindus Batch deviated from Brown Example 1.

Exelixis argues that the Girindus Batch, which resulted in 1-1 "levels as high as 411 ppm

[11] Nor can Exelixis claim that a POSA would need explicit examples, considering the '440 and '015 patents themselves do not identify any specific pharmaceutical compositions or methods of treating kidney cancer, despite having claims covering them. DFF ¶¶ 91, 94.

or even 600 ppm," was "made with the Brown Process." Resp. 42, 46-47. This is premised on a word game. Exelixis lumps the Regis and Girindus batches together based on its FDA submissions stating they were prepared using the "A-2" process." *Id*. at 42, n.15. But Dr. Lepore went beyond the labels and compared the "step-by-step" detailed synthetic schemes and narrative descriptions of each process. DFF ¶¶ 137. In doing so, Dr. Lepore identified numerous Girindus "deviations"—i.e., "major changes that fundamentally change the procedure" (Tr. 295:6-10)—from Brown Example 1. DFF ¶¶ 164-165. Exelixis concedes there were "nine Girindus deviations" but argues they were "still within the scope of the Brown Process." Resp. 48. But Exelixis never explains what the "scope of the Brown Process" is or how to determine if something is within it.

Exelixis' attempts to explain away Girindus' deviations also fall short. For example, Exelixis argues that the deviations "were made to … reduce [overall] impurities." Resp. 48. But the claim requires a limit on the 1-1 impurity. And one of the deviations skipped an entire purification step that Drs. Lepore and MacMillan agreed would have purged the *claimed* 1-1 impurity, leaving only a "very small amount" remaining. DFF ¶ 144; *see also* DFF ¶ 182. Exelixis downplays other deviations because they "centered *around intermediate steps* in the Brown Process which, according to Exelixis' studies, had no role in the formation of the 1-1 impurity." Resp. 48. But Exelixis cites no "studies" with this conclusion. To the contrary, Exelixis admits elsewhere that Girindus' intermediate-step deviations *did* have a role in formation of the 1-1 impurity: "during the multi-step A-2 Process … the 1-3 intermediate material decomposed to form large amounts of the 1-1 impurity." Resp. 42; RFOF ¶ 49.[12] Dr. Lepore provided unrebutted

[12] Exelixis argues that the 1-1 impurity formed in "large amount" during the "A-2 Process" and specifically with respect to the 1-3 intermediate material. Resp. 42. While cast as an issue with the "A-2 Process," in fact this was only an issue with the Girindus process because Girindus was the only process that resulted in "large amounts of the 1-1 impurity." RFOF ¶ 48.

testimony that Girindus deviated at this same 1-3 step—"[i]nstead of going from 1-3 to 1-4, [Girindus] went from 1-3 to something else." Tr. 297:19-298:1; DDX(Lepore)-31. Because Girindus did not "faithfully follow" Brown Example 1, its results are "not probative of what would inevitably occur if [it] were followed." *Merck & Cie v. Watson Lab'ys, Inc.*, 125 F. Supp. 3d 503, 513 (D. Del. 2015), *rev'd on other grounds*, 822 F.3d 1347 (Fed. Cir. 2016).

2. The Regis Batches faithfully followed Brown Example 1.

Exelixis' fallback argument asks that the Regis Batches also be disregarded because, "[l]ike Girindus, Regis also varied its production parameters." Resp. 48. Exelixis' only support is a vague statement that some "processing and reagent changes were implemented" for one batch. Resp. 48; PTX-10.9. But the exhibit does not detail any such "changes," let alone call them "deviations." *Id*. Instead, the text provides a detailed narrative of the Regis synthetic process, which Dr. Lepore compared to Brown Example 1 and concluded was the same. DFF ¶ 137. If Exelixis had evidence showing that Regis actually deviated, it would have confronted Dr. Lepore with it at trial. As a further fallback, Exelixis argues that "the Brown Process allows for variation, using the term 'approximately,'" and that "some variability would inevitably occur." Resp. 47, 49-50. But there is no evidence of any meaningful variability using the Brown Example 1 process. DFF ¶ 158.[13]

3. Expert testimony supports a finding of inherency.

Exelixis also argues that three Regis Batches is too small a "sample size" to "prove" inherency. Resp. 50. But no case requires any specific number of examples to prove inherency.

[13] That "the A-2 Process did not consistently produce API *at 2-12 ppm* as seen with the B-2 Process" (Resp. 46) misses the point. The claim does not require the 1-1 impurity at levels between 2-12 ppm, only less than 200 ppm. And Exelixis again conflates the "A-2 Process/Brown Process" labels to suggest there is variability that does not exist in the Regis Batches. Only by including the Girindus batch under the "A-2 Process/Brown Process" label can Exelixis argue that the "Brown Process did not consistently contain low levels of the 1-1 impurity." Resp. 46.

Rather, inherency is found where there are examples demonstrating the inherent result coupled with expert testimony confirming the underlying scientific principles. *Compare Hospira, Inc. v. Fresenius Kabi USA*, 946 F.3d 1322, 1330 (Fed. Cir. 2020) (there was "expert testimony that concentration does not affect the stability of dexmedetomidine.") *with Hospira, Inc. v. Amneal Pharms.*, 285 F. Supp. 3d 776, 800 (D. Del. 2018) (there was "no expert testimony regarding the scientific principles underlying its inherency argument"). Here, MSN has provided both.

Exelixis claims that MSN has not provided a scientific explanation for why "the Brown Process does not form the 1-1 impurity as a degradation product." Resp. 50-51. Not so. Dr. MacMillan testified that cabozantinib is a "very, very, very stable compound." Tr. at 661:15-18; *cf. Fresinius*, 946 F.3d 1330 (expert testimony that "dexmedetomidine is a very stable drug" supported inherency). And he explained that a POSA "would not [] expect[] the 1-1 impurity to form as a degradation product based on the strength of the chemical bond in cabozantinib that would need to break to form the 1-1 compound" and therefore a POSA "wound not have expected the 1-1 impurity to appear" in API synthesized according Brown Example 1. Resp. 53; Tr. 661:1-663:11. Drs. Myerson and Donovan agreed. DFF ¶ 148; Tr. 394:14-395:10 (Donovan).

Exelixis now argues that Dr. MacMillan merely testified a POSA "reviewing Brown *would not have expected* what Exelixis in fact discovered … that the 1-1 impurity *formed*, as demonstrated by Exelixis' work." Resp. 51. But there is no evidence that Exelixis' work "discovered" the 1-1 impurity formed in any meaningful amount (and certainly not more than 200 ppm) *when the Brown Example 1 process was followed*. Rather, as Dr. MacMillan clearly stated, "looking at the synthetic scheme, Scheme 1 in Brown," the POSA would not have "expected the 1-1 impurity to form" as a degradation product. Tr. at 661:1-4. And "at the end of the [Brown Example 1] process," a POSA would expect to find a non-detectable but non-zero amount of the

1-1 impurity (Tr. 680:2-10)—exactly what was found in the Regis Batches. *See* DFF ¶¶ 160-162.

B. It would have been obvious to a POSA to produce cabozantinib (L)-malate essentially free of the 1-1 impurity using recrystallization.

Alternatively, it would have been obvious to use recrystallization to produce API that was essentially free of the 1-1 impurity even if Brown Example 1 did not inherently produce it.

1. FDA guidance would have motivated a POSA to identify and control for the 1-1 impurity.

There is no dispute that prior art FDA guidance documents would have motivated a POSA to identify and control for the 1-1 impurity. DFF ¶¶ 170–176. Exelixis' only response is to mischaracterize Dr. Lepore's testimony. He did not testify that "a POSA would have been motivated to control for the 1-1 impurity because it was a starting material … that would have been *expected to carry through to the final cabozantinib (L)-malate product*," as Exelixis claims. Resp. 41, 52. He explained that regardless of whether the 1-1 starting material carries through, a POSA would have identified 1-1 as a GTI, and FDA guidance would have required controlling it because the guidance "applies to known starting materials." DFF ¶ 172. Exelixis has no response. Dr. MacMillan conceded that he did not consider any FDA guidance on starting material impurities. Tr. 681:21–682:8. And Dr. Myerson admitted that a POSA would have understood that because the 1-1 impurity was a GTI it needed to be "minimize[d]." Tr. 771:17-772:3; 755:13-23.

2. A POSA would have been motivated to use recrystallization with a reasonable expectation of success.

A POSA would have reasonably expected for recrystallization to successfully purge the 1-1 impurity, because FDA guidance also provided the solution if the GTI levels were too high: changing purification routes to "maximize the removal of the relevant impurity" such as by adding a recrystallization step. DFF ¶¶ 115, 178. Exelixis responds that "MSN failed to identify any reference describing the use of recrystallization to obtain purity at the extremely low levels of the

patented invention, i.e., under 200 ppm." Resp. 53. But Dr. Lepore testified that "the literature abounds with examples" of successful recrystallizations, and he explained that the Robinson reference discloses a recrystallization that purged a GTI down to "less than 1 ppm." DFF ¶ 117.

In response to unrebutted testimony about the widespread use of crystallization as a "conventional" and "highly effective method," (D.I. 169, 28-29; DFF ¶¶ 113-117), Exelixis turns to Dr. Myerson's testimony that some cases can be "challenging to achieve the claimed purity levels by recrystallization due to the structural similarity of the 1-1 impurity and the API." Resp. 53-54. But he offered no scientific basis to conclude that the 1-1 impurity is structurally similar to cabozanitinib (L)-malate such that crystallization would not be expected to work.[14] And even if structural similarity could make recrystallization ineffective in *some* instances, "the expectation of success need only be reasonable, not absolute" nor "guaranteed." *Pfizer,* 480 F.3d at 1364.

Exelixis' "real world" development "efforts" are not prior art, and thus not relevant. Resp. 54. Moreover, Exelixis omits that its development *did* include "[a] recrystallization step [that] was introduced in order to minimize the levels of GTIs" like the 1-1 impurity. PTX-35.12. Dr. Wilson explained this step was added because "recrystallization is the technique that's used to purify solid crystalline materials" and is a "general principle of purification." Tr. 572:2-21.

C. A POSA would have been motivated with a reasonable expectation of success to formulate a cabozantinib (L)-malate product free of the 1-1 impurity.

As Dr. Myerson conceded, formulating the claimed formulation would have been routine after starting with API with low ppm levels of the 1-1 impurity. DFF ¶¶ 193-196; Tr. 773:7-24 (POSAs could "use known techniques … [t]o make the pharmaceutical composition" without

[14] Nor can Dr. Myerson's conclusory opinion be reconciled with his own (and Dr. MacMillan's) earlier testimony explaining that crystallization would be expected to work during step one of the Brown Example 1 Process to purge 1-1 starting material from the (structurally similar) 1-2 intermediate. *See* DTX 291.25; Tr. 679:6-22 (MacMillan); 709:5-14 (Myerson).

"anything additional that would control for the 1-1"). Exelixis argues that the prior art did not disclose the 1-1 impurity was genotoxic. Resp. 45. But an impurity need not be identified in the prior art for there to be motivation to control it. In *Purdue Pharma v. Accord Healthcare*, "8α" (which caused an impurity) was "not disclosed in the prior art," but this Court agreed that "the discovery of 8α itself would have been routine" and therefore a POSA would "seek to reduce [] 8α." 2023 WL 2894939, at *22 (D. Del.).[15] So too here. A POSA would have identified the 1-1 impurity as potentially genotoxic and routine testing would have confirmed it. DFF ¶¶ 170-176.

A "formulator would have learned [that 1-1 was a GTI] from the chemists" and been motivated to control it during formulation, ensuring that no toxic substances formed during formulation. Tr. 397:3-16; DFF ¶¶ 130-134, 189. Dr. Myerson agreed, conceding that the FDA requires "control[ling] for genotoxic impurities in a formulation," using known analytical techniques to determine whether the 1-1 impurity forms during "the manufacture or storage" of the product. Tr. 764:17-768:22; DFF ¶¶ 190-193. That these tasks are routine explains why the '349 patent does not even describe how to perform them, stating merely that the claimed compositions are "prepared according to methods available to the skilled artisan." DFF ¶ 195.

Exelixis' arguments on reasonable expectation of success are unavailing for the same reasons. Resp. at 56. Dr. Donovan explained that a formulator would have evaluated "the structure of cabozantinib (L)-malate" and not seen any "chemical indicators" that would cause concern. Tr.

[15] Exelixis further distinguishes *Purdue* because "the FDA had asked opioid manufacturers to reduce impurities of this kind," but "in contrast, … no FDA guidance identified the 1-1 impurity as problematic." Resp. 57. That distinction fails. The 2002 "FDA letter" in *Purdue* "concern[ed] a different product" but caused motivation because the "issue [wa]s general and will affect all products." 2023 WL 2894939, at *19-20. By the 2011 priority date here, that general motivation also existed in the 2008 FDA guidance requiring all GTIs at low PPM levels. DFF ¶¶ 106-07. Moreover, in *Purdue*, a "suspicion" existed "even before" the FDA letter given the impurities' "structure"—the same suspicion that exists for 1-1 given its structural alerts. *Id.*; DFF ¶ 175.

394:14-395:10. Exelixis' "real-world evidence" speculating that "*certain* manufacturing conditions … *could* lead to formation of the 1-1 impurity" (Resp. at 40, 46, 48, 50) is irrelevant; it is not prior art. Nor are "accelerated conditions," which Dr. Shah explained are "higher temperature and humidity," relevant to what a POSA would expect under the *actual* manufacturing conditions. Tr. 606:25-607:3. Exelixis' argument that MSN did not *prove* "a final formulation would have necessarily been [] pure" because certain conditions "*could* lead to increased impurity levels" (Resp. 55) conflates reasonable expectation of success with inherency.

V. NO OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS

Exelixis has failed to present persuasive evidence of secondary considerations.

Nexus. Exelixis presented the same nexus argument in *Cabozantinib I* as it does here. It has not demonstrated that any objective indicia relate to purportedly nonobvious aspects of the asserted claims as opposed to the known uses and efficacy of the cabozantinib compound.

Blocking Patent. Exelixis cannot dispute that the '473 patent and its published parent application blocked entities other than Exelixis from pursuing commercialization of cabozantinib beginning in 2005; MSN's experts' testimony went unrebutted. DFF ¶¶ 202, 203. That generic companies later developed products under the Hatch-Waxman framework "is not evidence of commercial success that speaks to the non-obviousness of patent claims." *See Galderma Labs, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013).

Long-Felt, Unmet Need. Under Exelixis' misapplied view of long-felt, unmet need—that there was a "long-felt unmet need for a safe and effective cancer treatment" (Resp. 58)—every FDA-approved cancer therapy would support a finding of non-obviousness. *See also* Tr. 961:23-962:2. But at most, cabozantinib offered only an "incremental improvement" over other available therapies, representing a difference in "degree" and not in "kind." Tr. at 996:8-11 (Mega); DFF ¶ 209; *Bristol Myers-Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

There was no evidence that Cabometyx represented the type of "huge paradigm shift" in treatment that Exelixis' cited cases suggest meet a long-felt, unmet need. *See Pfizer*, 71 F. Supp. 3d at 475; *see also UCB*, 201 F. Supp. 3d at 538. Instead, earlier TKIs "represented a really profound advancement" (Tr. 993:10-994:10), and cabozantinib was just another alternative (Tr. 996:16-21).

Commercial Success. Mr. Tate wholly failed to consider development and commercialization costs necessary to bring Cabometyx to market, making it impossible to evaluate its success or profitability based solely on gross revenue. DFF ¶ 218. And without presenting any objective definition of success, Mr. Tate had no basis for comparing Cabometyx sales, prescriptions, or market share and declaring it "successful." DFF ¶¶ 217, 219.

Unexpected Results. Exelixis' argument that crystalline cabozantinib malate resulted in "unexpected results" is legally flawed. Resp. 38. Here, unexpected results must be compared to the reference patent. *See In re Pasteur*, 2023 WL 8609987, at *5 (Fed. Cir. 2023). Crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib. DFF ¶ 67. Thus, any attribute of crystalline (L)-malate is a latent property within the scope of the reference claim, and not an unexpected result. *See id.* at *3 ("discovering new properties of [reference claim] does not render the instant claims patentable."). And if a POSA had *no expectation* of what the "suite of properties" for any salt will be before it is formed, as Exelixis claimed (Tr. 828:3-6 (Koleng), 889:4-6 (Trout)), then malate salt's ultimate properties cannot be *unexpected*. *Pfizer*, 480 F.3d at 1371.

Finally, the only expert testimony was that cabozantinib (L)-malate was "very stable" and that it would be expected a formulation could be prepared that remained essentially free of the 1-1 impurity, as in claim 3 of the '349 patent. DFF ¶¶ 192, 225. Nor does Exelixis explain why the same results could not have been achieved using API from the Brown Example 1 prior art process.

VI. CONCLUSION

The Court should find that all of the asserted claims are invalid.

HEYMAN ENERIO
GATTUSO & HIRZEL LLP

/s/ Dominick T. Gattuso
Dominick T. Gattuso (#3630)
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@hegh.law

Attorneys for Defendants
MSN Laboratories Private Limited and
MSN Pharmaceuticals, Inc.

OF COUNSEL:

George C. Lombardi
Bryce A. Cooper
Kurt A. Mathas
Elizabeth E. Grden
Kevin J. Boyle
Brian L. O'Gara
WINSTON & STRAWN LLP
35 W. Wacker Drive
Chicago, IL 60601-9703
(312) 558-5600

Dated: February 20, 2024